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REVIEW

Multimodality imaging in cardiac amyloidosis: a primer for cardiologists

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Amyloidosis is a systemic infiltrative disease, in which unstable proteins misfold, form aggregates and amyloid fibrils which can deposit in various organs: heart, kidneys, liver, gastrointestinal tract, nervous system structures, lungs, or soft tissue. Cardiac amyloidosis (CA) diagnosis requires awareness, high level of clinical suspicion and expertise in integrating clinical, electrocardiographic, and multimodality imaging data. The overall scenario is complex and no single test emerges over the others, but different techniques are useful at various stages of the diagnostic workup. After a clinical suspicion of CA is raised by various non-imaging red-flags, eligible patients should undergo complete echocardiography and multiparametric cardiovascular magnetic resonance imaging. Even though the clinical suspicion of CA is confirmed by cardiac imaging, the accurate differentiation between the two most frequent and treatable amyloid types, i.e. light chain (AL) and transthyretin (ATTR) requires further work-up including phosphate scintigraphy. This article reviews the latest and essential data on multimodality imaging of patients with suspected or confirmed CA in a useful and practical manner for the general and imaging cardiologists.

Keywords amyloidosis • echocardiography • cardiac magnetic resonance • scintigraphy • multimodality imaging

Introduction

Amyloidosis is a systemic infiltrative disease, in which proteins with unstable structure misfold, form aggregates and amyloid fibrils which can deposit in various organs: heart, kidneys, liver, gastrointestinal tract, nervous system structures, lungs, or soft tissue.[1] The most frequent variants leading to cardiac amyloidosis (CA) are immunoglobulin light chains (AL amyloidosis) and amyloid transthyretin (ATTR amyloidosis, hereditary, or wild type), two CA subtypes with very different prognosis and management.[1]

CA is generally classified as a restrictive cardiomyopathy (RCM) due to its pathophysiology,[2] which frequently presents in a stage of left ventricular (LV) or biventricular hypertrophy with a small LV cavity and, sometimes in the late stages, dilatation. This is why it is also regarded as one of the hypertrophic cardiomyopathies (HCMs) phenocopies.[3]

Distinguishing CA from the broad diagnostic umbrellas of RCMs or HCMs is essential because it would lead to targeted therapies which can improve prognosis of both AL and ATTR patients. Timely diagnosis of cardiac involvement and subtyping of the amyloid is very important, as prognosis and therapeutic options are influenced by cardiac infiltration. Moreover, cardiac involvement in AL amyloidosis is the main contraindication to high-dose chemotherapy and autologous stem cell transplant, which has been effective in increasing the 5-year survival in the AL population.[4]

Although cardiac biopsy is considered the gold standard diagnostic test to confirm and type amyloidosis, it is not routinely performed in clinical practice due to its invasive nature and limited availability. Non-invasive imaging is a valuable alternative, being able to detect features strongly suggestive of CA.

We aim to describe the role of echocardiography, cardiovascular magnetic resonance (CMR), and scintigraphy in diagnosing, typing, and prognostication of patients with suspected or known CA.

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The pathobiological substrate for imaging findings

Understanding the pathophysiology of CA helps explaining the specific imaging findings. Extracellular amyloid infiltration leads to thickening of ventricular walls, increased ventricular stiffness, and consequently to high ventricular filling pressure. While many scientific reports focus on the presence of LV functional apical sparing, the pathophysiological mechanism underlying this finding is unclear. Rapezzi and Fontana[5] proposed recently that at least three main mechanisms can be hypothesized: less amyloid deposition at the apex compared to the base; this would lead to a lesser degree of resistance to deformation and, through a process of dynamic reciprocity, to an increased myocyte contraction, which may explain the relative preservation of apical contraction; the greater diversity of myocyte and matrix orientation at the apex compared to the base; and a greater tendency towards myocyte apoptosis in the basal segments related to the LV outflow tract turbulent flow and higher wall stress.

Atrial wall infiltration can also occur, leading to functional and electrical changes [e.g. atrial fibrillation (AF), atrial paralysis], as well as to an increased risk of atrial thrombus formation.[6,7] Amyloid can also deposit around the small coronary vessels, leading to coronary microvascular dysfunction or obstruction and subsequent myocardial ischaemia.[8] Direct light chain toxicity and non-inflammatory oedema may be responsible for cardiac dysfunction in AL amyloidosis in addition to interstitial infiltration.[9]

Of note, the imaging techniques which capture indirect targets of the CA pathobiology are used more frequently than those aiming at direct ones (*Figure 1*).

Echocardiography

The high accessibility, the ability to describe both cardiac structure and function, makes echocardiography the first-line tool in CA assessment.

The ventricles

The typical echocardiographic findings in CA include a small left ventricle with concentric hypertrophy, which can have a 'sparkling' or 'granular' myocardial appearance, with a preserved ejection fraction and biatrial enlargement. Often diagnosed when LV wall thickness is above 13 mm, it has been proven that values above 15 mm carry prognostic significance.[10] An important observation is the low electrocardiographic voltage-to-mass ratio. Using the Sokolow index as a measure of the electrocardiographic voltage, Carroll *et al.*[11] first noted a trend towards low values. When correlating it with echocardiographic LV hypertrophy (LVH), the authors noted an inverse correlation between voltage and muscle cross-sectional area in amyloidosis patients (*Figure 2*). However, in a wild-type ATTR (wtATTR) patient population Gonzalez-Lopez *et al.*[12] found low voltage only in a fifth of the cohort and 10% of the patients presented with LVH electric criteria.

Left ventricular ejection fraction (LVEF) is usually normal (>50%), however, it can progressively decrease in late stages of the disease. While rare, dynamic obstruction at the level of the LV outflow tract can be encountered. CA was diagnosed at pathology in 0.9% of patients undergoing myectomy for hypertrophic obstructive cardiomyopathy in a series from the Mayo Clinic.[13]

Of note, using only the above-mentioned conventional echocardiographic changes, around 20% of patients with systemic AL amyloidosis may be considered as not having cardiac involvement, as was shown in an early echocardiographic study almost three decades ago.[10] However, cardiac symptoms and death occurred in this CA subgroup during follow-up, stressing the importance of early diagnosis based on more sensitive parameters. For example, even at early stages subclinical systolic dysfunction can be detected using tissue Doppler imaging (TDI)—as myocardial systolic (S') and diastolic (e') longitudinal velocities are low in CA.[14]

Furthermore, subclinical systolic dysfunction, which precedes the onset of heart failure symptoms, can be detected by strain and strain rate imaging, even before TDI parameters are altered.[15] Using speckle tracking echocardiography, Phelan *et al.*[16] described regional variations in 2D longitudinal strain (LS) from base to apex, and defined a 'relative apical sparing' calculated as the ratio of apical LS to the sum of basal and mid LS. A relative apical LS of 1 was able to differentiate CA from HCM [sensitivity 93%, specificity 82%, area under the curve (AUC) 0.91], as well as CA from aortic stenosis (sensitivity 93%, specificity 82%, AUC 0.97) (*Figure 3*). Several other groups confirmed the good sensitivity and specificity of basal-to-apical LS ratio for differentiating CA from isolated arterial hypertension, Fabry disease, and Friedreich ataxia,[17] reporting however a rate of 32% false positive findings in hypertensive hearts. In order to minimize diagnostic inaccuracy, Pagourelias *et al.*[18] proposed a new approach taking into consideration the phenomenon of preserved LVEF with decreased LS, by using the LVEF to global longitudinal strain ratio (EFSR), which performed better in differentiating CA from other forms of cardiac hypertrophy with preserved ejection fraction, irrespective of the amyloid type.

Right ventricular (RV) hypertrophy and dysfunction were often described in CA patients, and associated worse survival; tricuspid annulus systolic excursion, with a cut-off <14 mm, is useful for assessing prognosis of CA patients.[19]

Assessment of LV diastolic function and filling pressures is essential in RCM and thus in CA, based on the current joint American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) document for the evaluation of diastolic function by echocardiography[14,20] (*Figure 4*). Of note, the diagnosis of RCM does not require the presence of a restrictive mitral inflow pattern,[14] as patients may rarely present with a Grade I diastolic dysfunction and move progressively to Grade II or III with worsening of the disease associated with the worst prognosis.[21] A combined approach including both the finding of a low LV basal LS and the presence of diastolic dysfunction parameters such as high E/e' >12[22] or short E-wave deceleration time <200 ms[17] appears to increase the discrimination value of echocardiography between CA and other hypertrophied hearts.

Newer techniques such as cardiac shear wave (SW) imaging were introduced to assess myocardial mechanics. A recent study showed that end-diastole SW velocities were significantly higher in patients with CA, which can be explained by myocardial stiffening.[23]

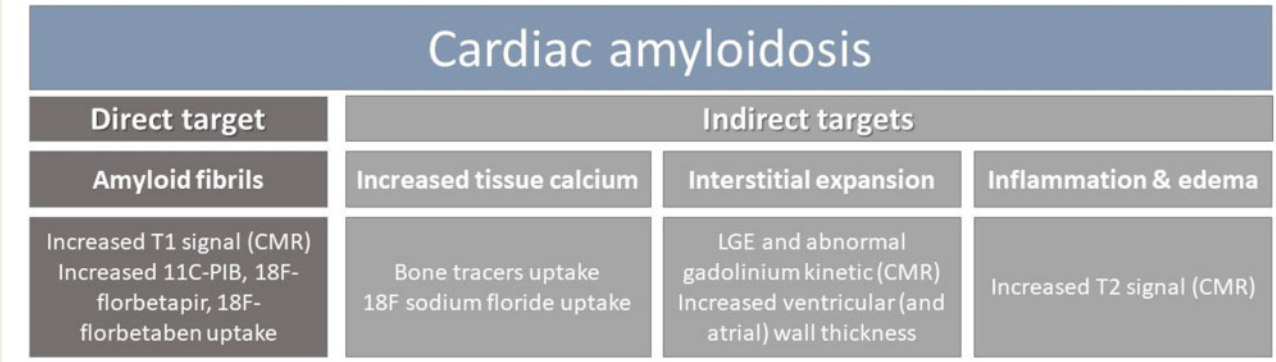

Figure 1 Imaging of cardiac amyloidosis and pathophysiology: direct and indirect targets.

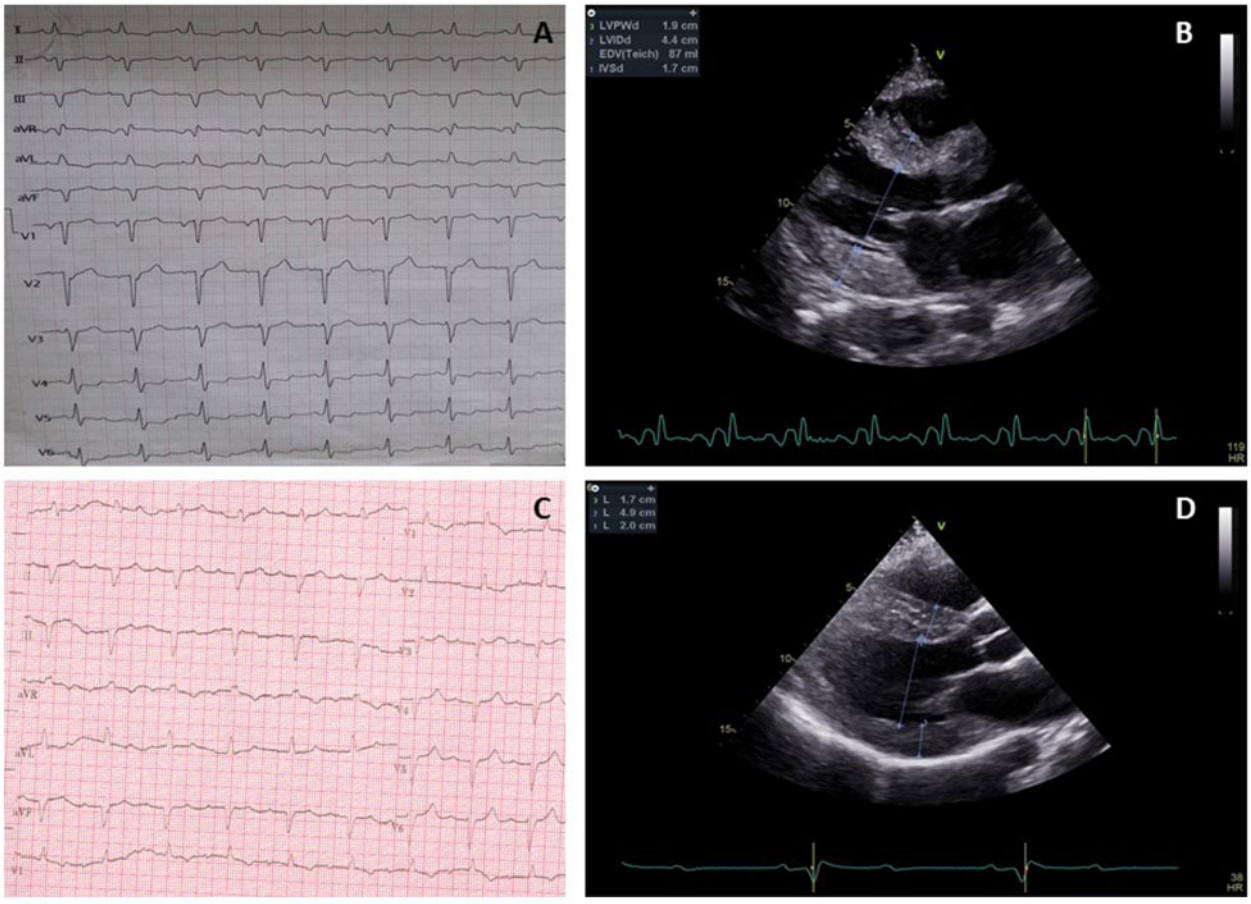

Figure 2 Abnormal LV voltage-to-mass ratio in two patients with cardiac amyloidosis: AL amyloidosis (*A* and *B*) and ATTR amyloidosis (*C* and *D*).

The atria

Increased LV stiffness as well as increased RV pressures lead to biatrial dilatation which is a common feature of CA, especially in the severe heart failure subgroup, representing an independent predictor of overall survival.[24,25] Beyond dilatation as a haemodynamic response, the atrial walls of CA patients undergo extracellular amyloid infiltration.[7] Increased atrial septal thickness was present in 60% of amyloid patients in one of the first echocardiographic studies.[14,26]

Severe involvement is characterized by a small or absent mitral inflow A wave as an expression of impaired or absent atrial contractility

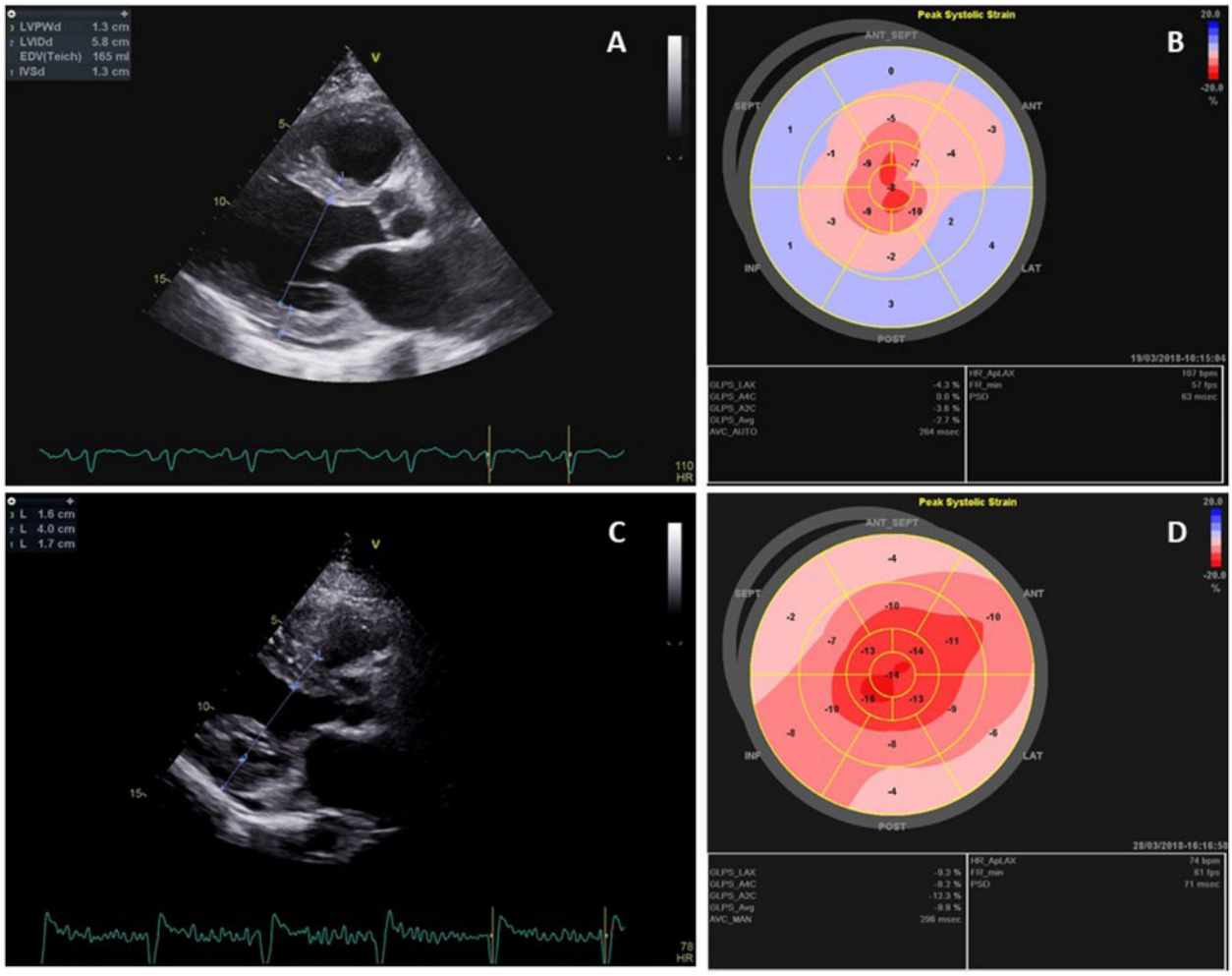

Figure 3 (*A* and *B*) Severely depressed myocardial deformation with apical sparing on LV map of myocardial deformation in a newly diagnosed AL amyloidosis patient with mild LV hypertrophy (13 mm circumferential wall thickness). (*C* and *D*) Apical sparing in a patient with ATTR amyloidosis and moderate LV hypertrophy.

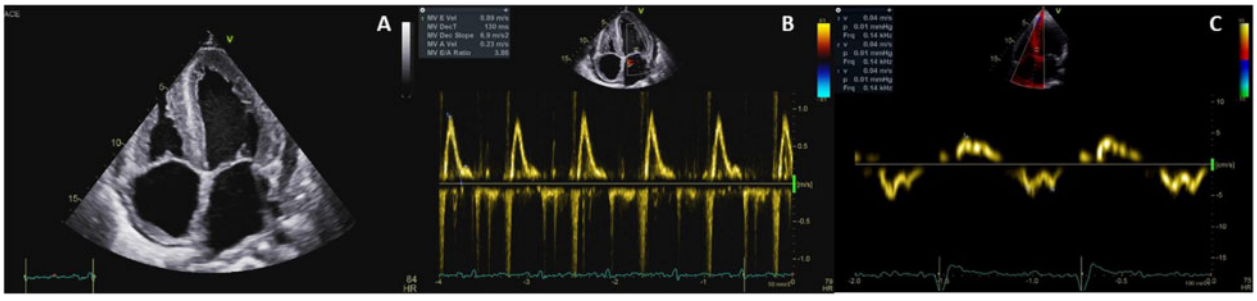

Figure 4 (*A*) Four-chamber view of a young woman recently diagnosed with ATTR amyloidosis, showing biatrial enlargement, thickened right atrial wall and inter-atrial septum, LV hypertrophy, and mild pericardial effusion. (*B*) Restrictive mitral flow pattern (*E*/*A* ratio of 3.86). (*C*) Tissue Doppler imaging of the mitral annulus with very low systolic and diastolic septal velocities and a *E*/*e*′ ratio of 22.

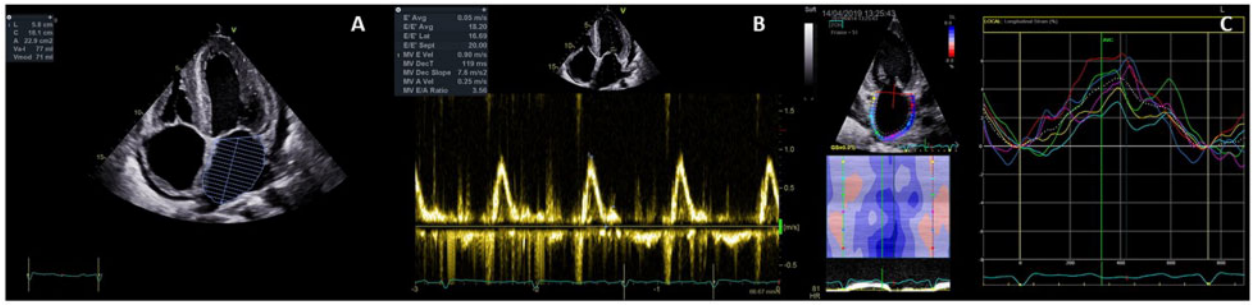

Figure 5 Left atrial dilatation (51.3 mL/m^2) (*A*), restrictive mitral flow pattern (*B*), and severely depressed left atrial strain (*C*) in a patient with AL amyloidosis.

as well as restrictive physiology.[27] The most robust technique for left atrial (LA) functional assessment remains the 2D strain imaging (*Figure 5*).[6,28] Nochioka *et al.*[6] recently showed that all the 2D speckle-tracking derived LA phasic functions were severely impaired in CA and highly correlated with LV deformation, being correlated with a greater impairment of LV systolic and diastolic function. Mohty *et al.*[29] also demonstrated the incremental prognostic value and high reproducibility of 3D measured peak atrial LS.

Absent atrial contractility can lead to intra-atrial thrombus formation even in sinus rhythm patients.[27,30] Awareness of this complication is crucial for timely initiation of anticoagulant therapy. A large autopsy study of patients with CA[31] reported a high incidence of intracardiac thrombosis (most frequently atrial), especially in AL patients, despite sinus rhythm and relatively preserved LVEF. The AL type, co-existence of AF, poor LV diastolic function, RV wall thickness, and higher heart rates were all independent predictors for systemic thromboembolism.

The valves and pericardium

The atrioventricular valves (mitral and tricuspid) can be thickened and stiff in CA patients; a thicker than 3 mm left-sided valve was found in 42% of AL patients undergoing echocardiography.[32] Usually, there is no significant regurgitation, but left heart valve thickening was associated with worse functional class, LV systolic and diastolic function, more advanced disease stage and increased all-cause mortality in AL patients.[32]

Pericardial effusion is often present, most frequently in small amount,[33] but if present it carries a negative prognosis.[34]

Cardiovascular magnetic resonance

Due to its high-quality images, tissue characterization capabilities and non-irradiating nature, CMR is currently considered the imaging tool of choice for diagnosing and characterizing CA.[35]

Morphological and functional data from CMR

Due to its adequate spatial resolution and sharp contrast independent of the body habitus, CMR is a useful alternative in patients with suspected or definite CA and poor acoustic window. Apart from the classical appearance of concentric LVH, there are other recognized CA, such as asymmetrical thickening or non-thickened LV walls. LV mass has been reported to be markedly increased in ATTR amyloidosis compared to the AL type.[36] The RV wall may be thickened, and the ejection fraction of both ventricles may be normal or decreased. The LA walls and interatrial septum may also be thickened, and in this regard non-contrast CMR can easily differentiate between a lipomatous hypertrophy and an infiltrative thickening of the interatrial septum.

Early gadolinium enhancement imaging

Static early gadolinium enhancement (EGE) images are usually acquired in the first 3 min after gadolinium-based contrast agent (GBCA) administration. As the contrast agent is not able to penetrate the avascular structures, this technique is useful for the detection of intracavitary thrombi and areas of microvascular obstruction (MVO). Coronary MVO has been clearly demonstrated in the setting of CA by histological studies,[37] while EGE imaging permits in vivo identification of MVO (*Figure 6*).

Late gadolinium enhancement imaging

Late gadolinium enhancement (LGE) is the cornerstone and the gold standard imaging technique for CA patients whose kidney function allows the administration of GBCA. Gadolinium is a purely extracellular agent, and thus in CA, its volume of distribution is proportional to the interstitial expansion secondary to amyloid deposition.

The typical LGE pattern in CA is represented by diffuse myocardial hyperenhancement, with a dark blood pool (*Figure 7*). Some patients display circumferential hyperenhancement only in the subendocardium while in others it is transmural[38] (*Figure 7*). Fontana *et al.*[39] hypothesized that the patterns of LGE constitute steps in a continuous evolution of amyloid deposition, with progression from no LGE,

to subendocardial LGE as an intermediate phase, and finally to transmural LGE.

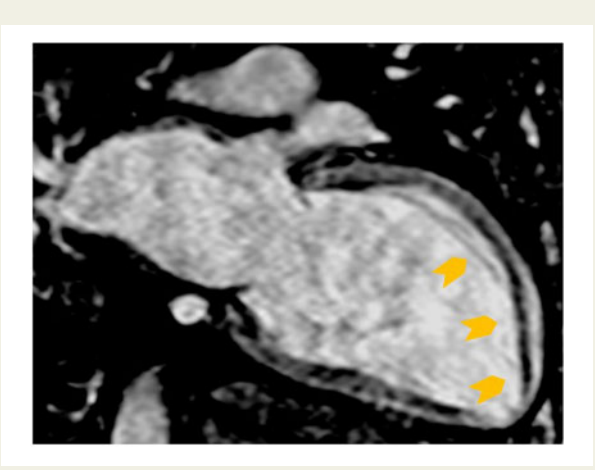

Figure 6 EGE two-chamber view in a patient with AL-type cardiac amyloidosis (image is acquired 1 min after GBCA). A thin, hypoenhanced area is seen in the subendocardium (yellow arrowheads), surrounded by normally enhanced myocardium. The subendocardium appears dark because the GBCA is not able to penetrate it—highly suggestive of MVO.

Another sign of amyloid deposition is the abnormal myocardial and blood-pool gadolinium kinetics, demonstrated in the inversion time (TI) scout sequence (*Figure 8*).[40] This abnormal contrast handling on TI scout, defined as myocardium nulling before blood, is considered a type of global LGE even if no hyperenhanced areas are seen.[38,40,41]

Due to difficulty in nulling the myocardium, a TI chosen incorrectly by the operator may lead to inaccurate estimation of LGE.[39] With phase-sensitive inversion recovery (PSIR) imaging, the tissue with the least gadolinium will always be nulled and thus PSIR reconstruction images are more reliable and should always be used to assess LGE in CA.[39] Due to the complexity of these findings, in many patients LGE imaging is not always straightforward, requiring solid expertise both of the operator and of the reporting physician. The sensitivity and specificity of the classical LGE-based CMR protocols were reported to be 85% and 92%, respectively.[42]

When present, LGE is a strong predictor of mortality in patients with CA.[39,41,43,44] Patients with no LGE have the most favourable prognosis (≈92% chance of survival at 24 months), while patients with transmural LGE carry the worst prognosis (61% chance of survival at 24 months).[39] Within the transmural pattern, the median survival is longer for ATTR than for AL, suggesting that amyloid deposition is not the only mechanism of the disease, but the superimposed toxicity of the light chains in AL amyloidosis may also play a role in defining the prognosis of CA patients.[39]

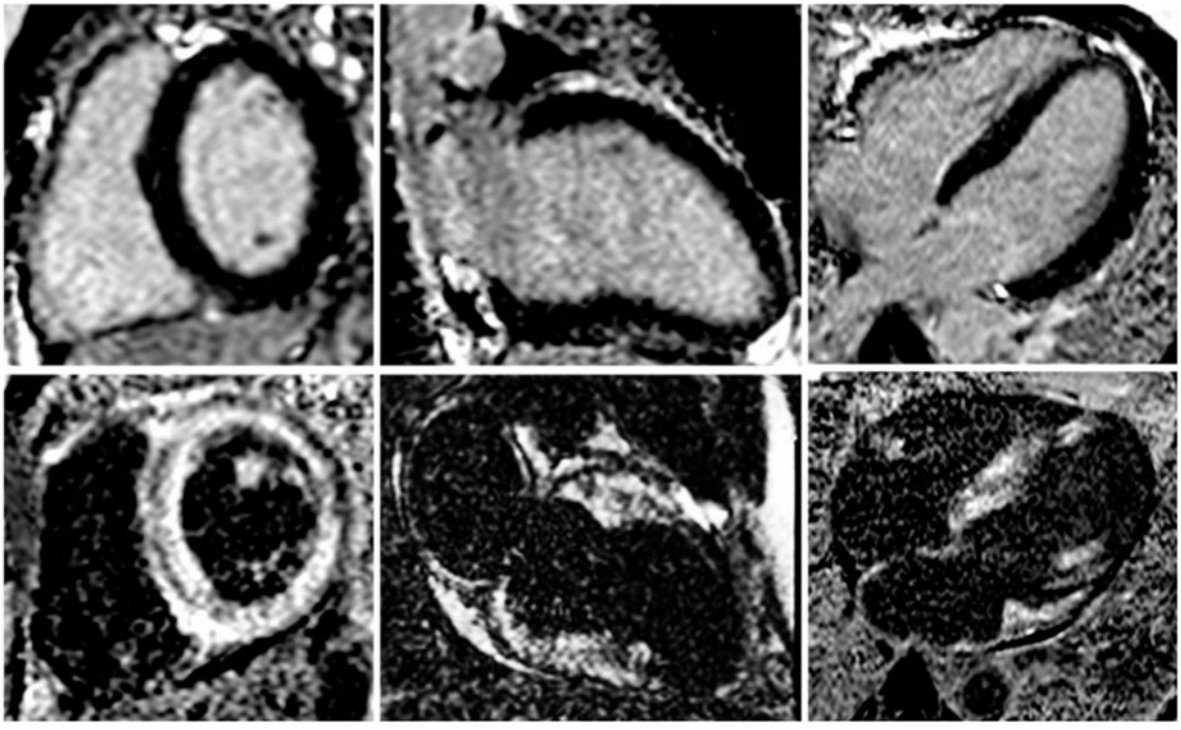

Figure 7 LGE imaging in a normal subject (upper row) and in a subject with confirmed AL-type cardiac amyloidosis (lower row). Short axis, two-chamber, and four-chamber views are shown (from left to right). The myocardium of the healthy subject appears black, without any areas of hyperenhancement, and the blood pool is bright. On contrary, the patient with amyloidosis displays transmural, circumferential hyperenhancement localized predominantly at the base of the heart, with apical sparring; in this case the blood pool is dark.

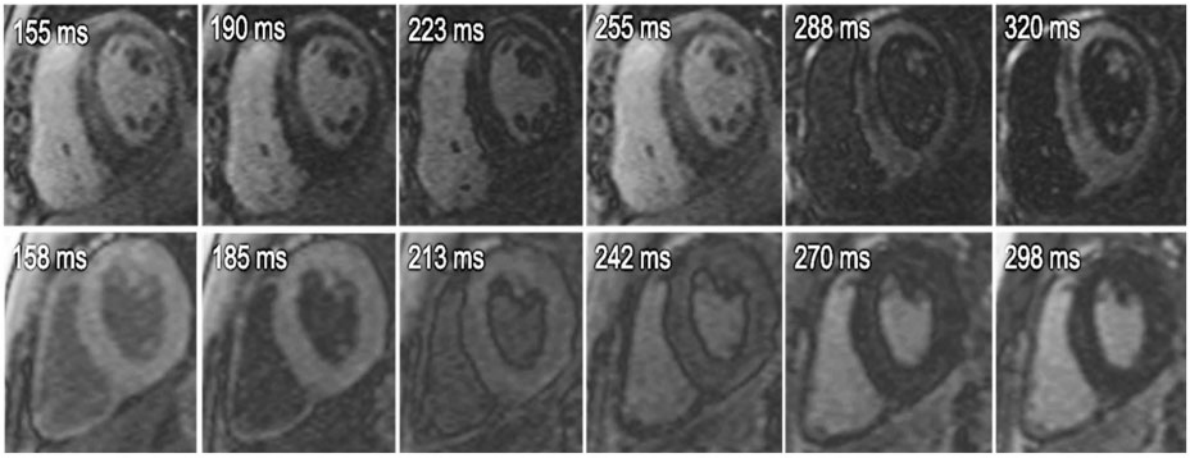

Figure 8 TI scout sequences in a patient with confirmed AL-type amyloidosis (upper row) and in a normal subject (lower row). In amyloidosis, the myocardium contains more GBCA than the blood pool, and thus it reaches the null point earlier than the blood pool, at around 223 ms. On contrary, in the case of the healthy subject, blood pool becomes black first, and then, the myocardium reaches the null point at 298 ms. Inspection of the TI scout pattern is always useful for the CMR diagnosis of cardiac amyloidosis by identifying abnormal Gadolinium kinetics.

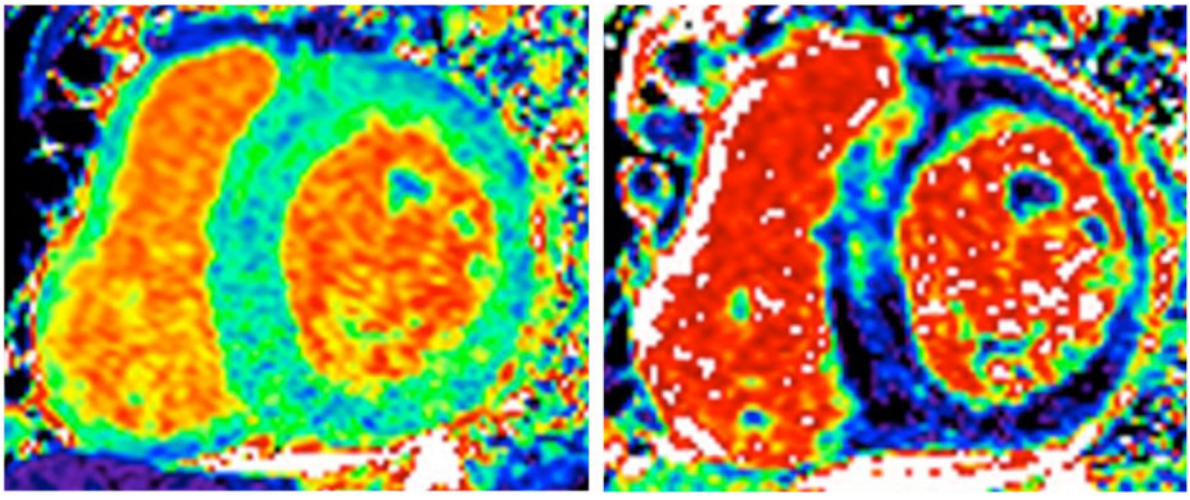

Figure 9 T1 maps of short-axis slices before (left) and after (right) GBCA administration, at 1.5 T, in a patient with confirmed AL-type cardiac amyloidosis. The native septal T1 was 1262 ms, while the septal post-contrast T1 was 426 ms, resulting in a ECV of 76%.

Native T1 mapping

T1 mapping represents a pixelwise illustration of myocardial T1 relaxation times—an intrinsic property of each tissue[45] (*Figure 9*). Native myocardial T1 enables diagnosis of CA to be made without the need for GBCA administration, because very high T1 values are characteristic for CA.[46] As such, T1 mapping is an essential technique in patients with kidney failure who cannot receive contrast.

Post-contrast T1 mapping

Integration of native T1 with post-contrast T1 values permits non-invasive quantification of extracellular volume fraction (ECV),[45] which is currently employed in clinical studies to define the amyloid burden[35] and correlates well with 99mTc-DPD scintigraphy.[47]

T1 mapping and ECV assessment by CMR are among the earliest imaging biomarkers for cardiac amyloid deposition. Patients with systemic amyloidosis have markedly increased myocardial native T1 and ECV values,[38,43,47,48] even in the absence of LGE.[38,39,43]

The results of studies reporting the predictive value of native T1 mapping are conflicting.[43,49] On the contrary, the high predictive value of ECV proved to be consistent across the studies. An ECV >44% remained independently prognostic for mortality in AL amyloidosis even in patients with a similar LGE pattern.[43] Accordingly, ECV is a better prognostic marker than native T1 mapping and

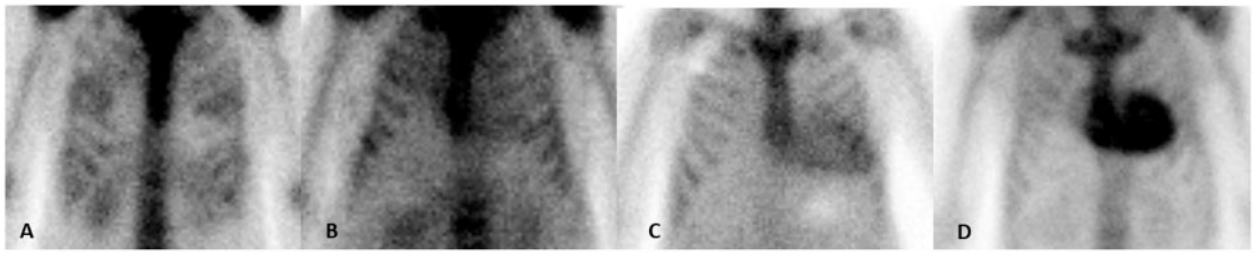

Figure 10 Bone scintigraphy: Perugini grading of myocardial uptake illustrating AL (*A* and *B*) and ATTR amyloidosis (*C* and *D*). The four panels correspond to the Perugini Grades 0–3, from left to right.

whenever possible T1 mapping with contrast administration should be performed.

T2 mapping

T2 imaging is a well-established non-contrast technique that quantifies the myocardial oedema in a pixelwise manner and illustrates it on a map. Recently, oedema was demonstrated using T2 mapping in both types of amyloidosis but to a larger extent in AL CA.[35] In the same study, T2 predicted mortality in AL amyloidosis and remained significantly predictive after adjusting for ECV and NTproBNP. Interestingly, there was no relationship between T2 and prognosis in ATTR amyloidosis, suggesting that oedema is a less important factor in the pathogeny of ATTR than AL amyloidosis.[35]

The place of CMR in the diagnostic work-up of CA in daily practice

Although CMR is considered the imaging tool of choice in patients with suspected or confirmed CA, currently, it is not clear whether it should be performed in all patients. Local availability of the technique and expertise should be taken into consideration. The following are well documented clinical scenarios in which CMR can be successfully included in the diagnostic algorithm:

- Patients referred to CMR for tissue characterization of an echocardiography detected LVH; in these patients, CMR can detect a definite pathognomonic pattern for CA (e.g. diffuse subendocardic LGE, increased native T1 values, increased ECV) or can suggest other specific LVH aetiologies;
- Patients with known systemic amyloidosis in whom early myocardial involvement can be detected by CMR T1 mapping techniques even before LVH development; and
- Patients with known CA in whom CMR can detect and quantify the associated myocardial oedema and amyloid deposition. These parameters have important prognostic value and the potential of accurate monitoring of disease response under specific treatment.

Radionuclide imaging for amyloidosis subtyping

While a combination of echocardiography, electrocardiography, and CMR can lead to the suspicion of CA, they cannot accurately contribute to the typing of the underlying amyloid. During the last decade, an important advance in CA imaging was brought by nuclear medicine.

Several phosphate derivatives tagged with [99mTc] including [99mTc]-pyrophosphate ([99mTc]-PYP), [99mTc]-methylene diphosphonate ([99mTc]-MDP), [99mTc]-hydroxy methylene diphosphonate ([99mTc]-HMDP), and [99mTc]-3,3-diphosphono-1,2-propanodicarboxylic acid ([99mTc]-DPD) have all been shown to effectively identify TTR-type CA.[50]

The initial Perugini grading system of myocardial uptake was based on a visual scoring of cardiac retention[51] which should be assessed at 3 h after tracer administration: Score 0—absent cardiac uptake and normal bone uptake; Score 1—myocardial uptake less than rib uptake; Score 2—myocardial uptake equal to rib uptake; Score 3—myocardial uptake greater than rib uptake with mild/absent rib uptake (*Figure 10*).[52] More recently, Hutt *et al.*[53] proposed a revised grading system, which also takes into consideration the soft-tissue uptake: Grade 0—no visible myocardial uptake in either the planar or cardiac SPECT-CT scan; Grade 1—cardiac uptake seen only by SPECT-CT, or minimal cardiac uptake (less intense than bones) evident on the planar scan and with no apparent reduction in intensity of the normal bone images; Grade 2—moderate cardiac uptake, greater in intensity than the bone uptake with apparent reduction of the latter on planar imaging; Grade 3—intense cardiac uptake with little or no bone uptake visualized on planar imaging; Grade 4—intense soft-tissue uptake partly or completely obscuring cardiac uptake on planar imaging.

Another quantification method, proposed by the guidelines for [99mTc]-PYP and evaluated at 1 h after tracer administration, uses the uptake ratio between the heart area and the contralateral area, with an H/CL ratio of ≥1.5 at 1 h.[54]

In differential diagnosis, 99mTc-DPD uptake is absent in unaffected control subjects, strong in TTR CA, and absent or weak in AL CA (with a H/CL ratio <1.5)[51,55,56,57] (*Figure 11*). Gillmore *et al.*[58] showed that the sensitivity of a positive (Grade 1, 2, or 3 cardiac uptake) scan alone for detecting cardiac ATTR amyloid deposits is >99% and the specificity of a positive scan (Grade 1, 2, or 3 cardiac uptake) for cardiac ATTR amyloid deposits is 68%, which was due almost entirely to cardiac uptake of tracer among patients with cardiac AL or (more rarely) cardiac apolipoprotein A-I amyloidosis. When associated with a negative assessment for plasma cell dyscrasia, a bone scintigraphy scan with abnormal uptake (Grade 2 or 3) has a specificity and positive predictive value of 100% for diagnosis of ATTR CA.[58] TTR

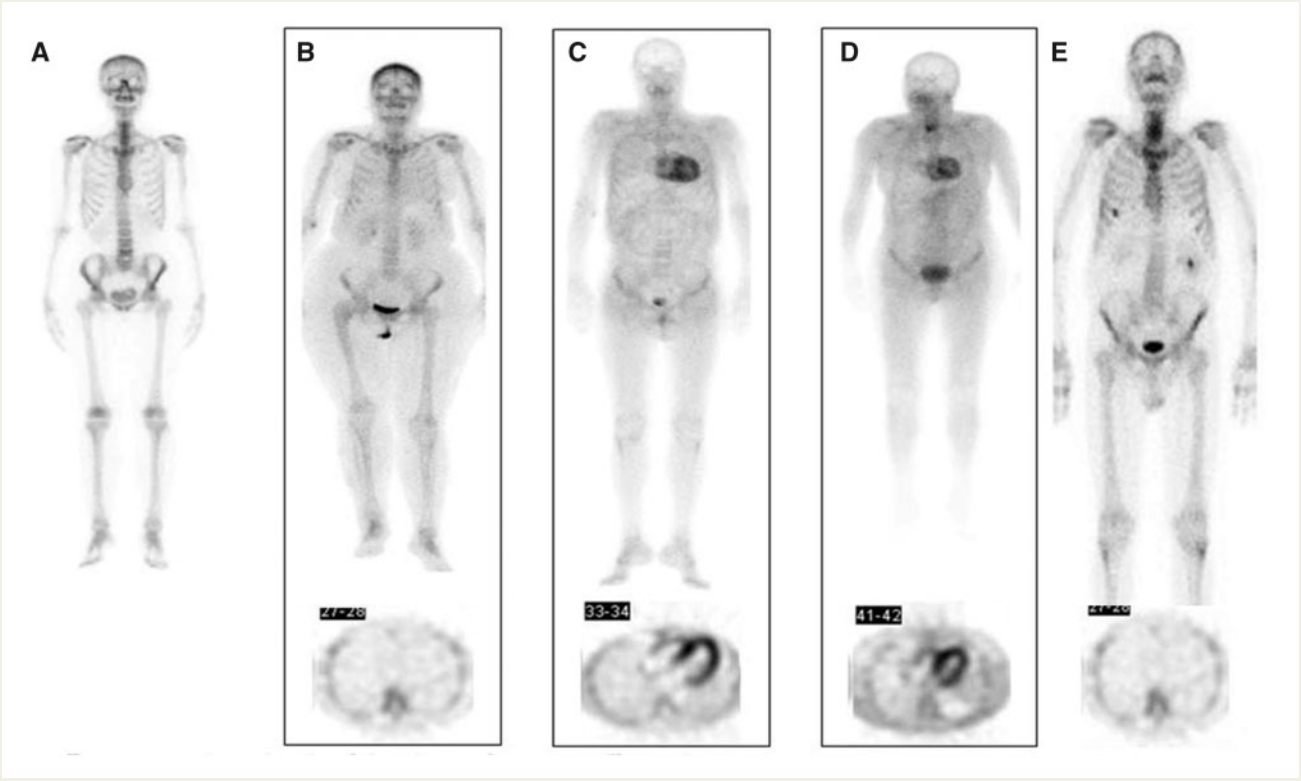

Figure 11 DPD sequences (180 min after DPD administration) in five different cases. (*A*) Normal subject. (*B*) AL cardiac amyloidosis: no DPD uptake. (*C*) hTTR (I68L) mutation with cardiac amyloidosis and intense DPD uptake (*D*) wild-type TTR cardiac amyloidosis and intense DPD uptake. (*E*) Hypertrophic sarcomeric cardiomyopathy with no DPD uptake.

genotyping is finally needed to differentiate wild-type from mutant ATTR CA. Of note, the study of Gillmore *et al.*[58] included patients with 35 different ATTR mutations. The rare situation of a false negative nuclear scan for ATTR CA had only been reported in association with limited histological subclinical cardiac ATTR amyloid deposits. However, a very recent report by Musumeci *et al.*,[59] which included a cohort of 40 TTR Phe64Leu patients, found a very low sensitivity (10.5%) of bone scintigraphy in detecting CA leading to a 37% diagnostic accuracy. While not being designed for providing and explanation for these discrepant findings, this observation shows that a critical look and further diagnostic tests are needed in the presence of high suspicion of cardiac involvement in hTTR patients with a negative bone scintigraphy.

Among TTR mutations carriers, 99mTc-DPD uptake can be detected before clear echocardiographic and electrocardiographic phenotype development.[56] This is very important for the follow-up strategy and treatment initiation in mutation-positive phenotype-negative relatives.[60]

Multimodality diagnostic algorithm

The diagnosis of CA requires awareness, expertise and a high level of clinical suspicion, with integration of clinical, electrocardiographic, and echocardiographic data with clinical and biological red flags (Supplementary data online). The overall scenario is complex and no single test emerges over the others, but different techniques are useful at different stages of the diagnostic workup[12,61] (Figure 12, Supplementary data online - *Figure*, *Table 1*).

While cardiac biopsy seldom appears as necessary when balancing risks and benefits, extracardiac sites can be used. One of the most common is abdominal fat aspiration, in which amyloid stains with Congo red dye to produce an apple-green birefringence when viewed under polarized light. However, it has a sensitivity of 80–90% for diagnosis of systemic AL amyloidosis, but only 45% and 15% for diagnosis of ATTRm and ATTRwt amyloidosis, respectively.[62] A negative fat aspirate does not exclude amyloidosis, and biopsy of rectal or salivary glands are alternatives with good diagnostic sensitivity.

Each of the three imaging techniques provides valuable prognostic information as mentioned above in the respective sections. As the introduction of CA specific therapies is relatively recent, currently, there is no reliable data regarding the role of serial imaging for monitoring the treatment response in CA. Further studies are required to evaluate the role of cardiac imaging for this specific indication.

Conclusions

Multimodality imaging is an essential tool in diagnosing CA. The stepwise use of various imaging modalities in conjunction with the clinical

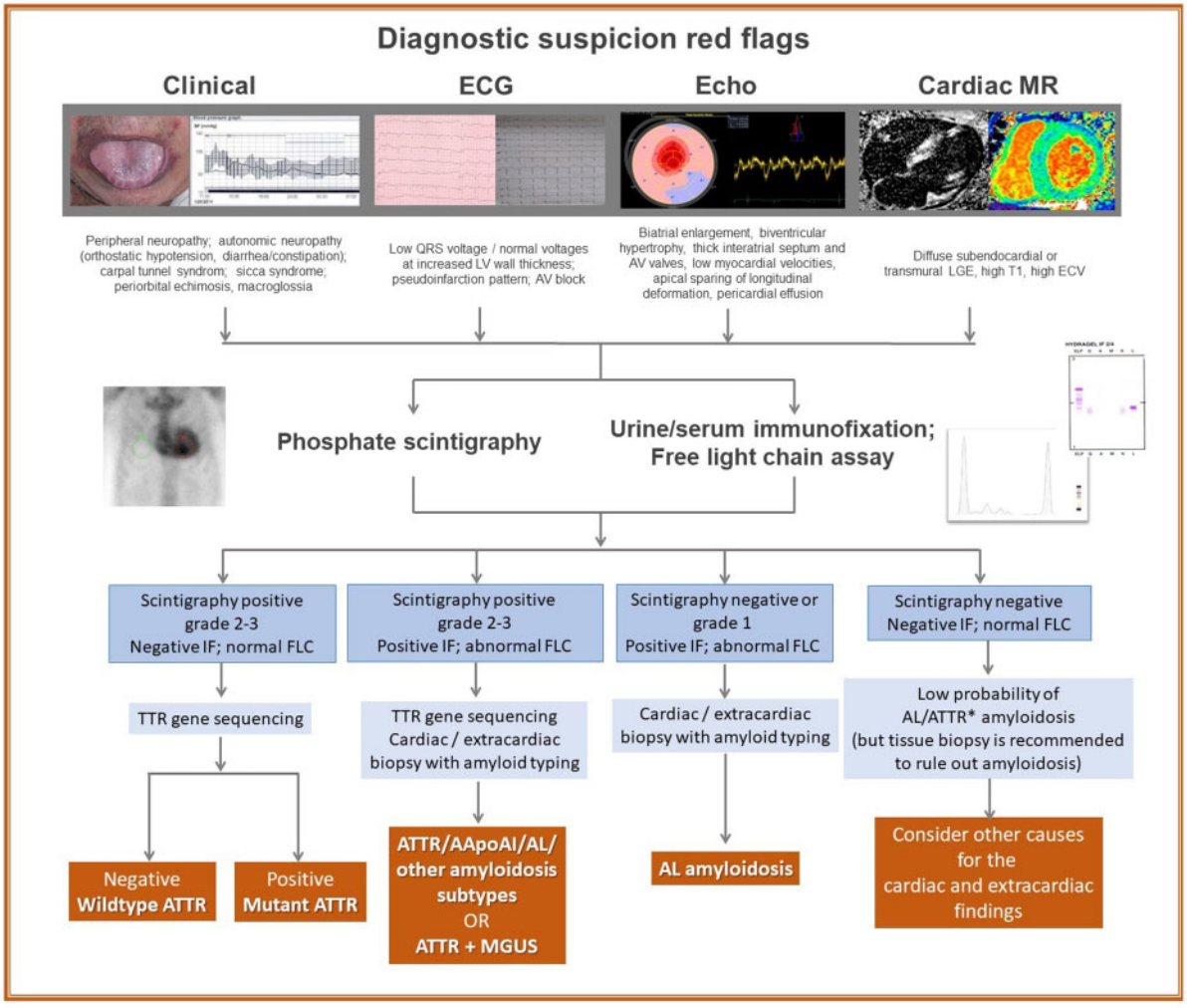

Figure 12 Diagnostic algorithm leading from the clinical suspicion for CA to the final diagnosis.

Table 1 Role of various imaging techniques in the different steps of cardiac amyloidosis diagnosis and management (modified after[61])

Phase of workup	Echocardiography	Cardiac MR[a]	Bone tracers scintigraphy[b]
Diagnostic suspicion	+++	++	+
Definite diagnosis	++	++	+++
Early diagnosis	+	+	+++
Functional evaluation	+++	+++	-
Prognostic stratification	+	+++	+
Amyloidosis burden	+	+++	+
Response to therapy	+	++	?

-, not useful; +, possibly useful; ++, useful, to be considered; +++, very useful, recommended; ?, unknown; ATTR, transthyretin-related amyloidosis; MR, magnetic resonance.
[a]Late gadolinium enhancement and native T1 mapping.
[b]For ATTR amyloidosis.

and laboratory data can bring on the diagnostic suspicion and hence fill the gap of disease awareness. The multidisciplinary teams for amyloidosis should therefore include cardiac imaging specialists.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: none declared.

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